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DOPAMINE MIDBRAIN NEURONS IN HEALTH AND PARKINSON'S DISEASE: EMERGING ROLES OF VOLTAGE-GATED CALCIUM CHANNELS AND ATP-SENSITIVE POTASSIUM CHANNELS

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Abstract—Dopamine (DA) releasing midbrain neurons are essential for multiple brain functions, such as voluntary movement, working memory, emotion and cognition. DA midbrain neurons within the substantia nigra (SN) and the ventral tegmental area (VTA) exhibit a variety of distinct axonal projections and cellular properties, and are differentially affected in diseases like schizophrenia, attention deficit hyperactivity disorder, and Parkinson's disease (PD). Apart from having diverse functions in health and disease states, DA midbrain neurons display distinct electrical activity patterns, crucial for DA release. These activity patterns are generated and modulated by specific sets of ion channels. Recently, two ion channels have been identified, not only contributing to these activity patterns and to functional properties of DA midbrain neurons, but also seem to render SN DA neurons particularly vulnerable to degeneration in PD and its animal models: L-type calcium channels (LTCCs) and ATP-sensitive potassium channels (K-ATPs). In this review, we focus on the emerging physiological and pathophysiological roles of these two ion channels (and their complex interplay with other ion channels), particularly in highly vulnerable SN DA neurons, as selective degeneration of these neurons causes the major motor symptoms of PD.

Key words: $Ca_v1.3$, D2-autoreceptor, KChip3, Kir6.2, voltage gated calcium channels, excitotoxicity.

Contents

THE DOPAMINERGIC MIDBRAIN SYSTEM

Dopamine (DA) releasing midbrain neurons are crucial for fundamental and complex brain functions, such as voluntary movement and goal-directed behavior, as well as cognition, emotion, reward, motivation, working memory, associative learning and decision making (Grace et al., 2007; Redgrave et al., 2010; Schultz, 2010a; Gerfen and Surmeier, 2011; Salimpoor et al., 2011; D'Ardenne et al., 2012; Chowdhury et al., 2013). Accordingly, dysfunctions of the DA midbrain system are associated with neurological and psychiatric diseases, such as schizophrenia, addiction, attention deficit hyperactivity disorder (ADHD) and Parkinson's disease (PD), the second most common neurodegenerative disease (Braak et al., 2004; Bjorklund and Dunnett, 2007; Dagher and Robbins, 2009; Stuber et al., 2010; Shulman et al., 2011; Bari and Robbins, 2013; Russo and Nestler, 2013; Sulzer and Surmeier, 2013; Brisch et al., 2014). The majority of DA midbrain neurons are located in two overlapping nuclei, the substantia nigra (SN, A9) and the ventral tegmental area (VTA, A10) (Schultz, 2010b). These neurons have widespread axonal projections to subcortical and cortical target areas, and display diverse electrophysiological properties *in vitro*

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Abbreviations: D2-AR, D2-autoreceptor; DA, dopamine; DBS, deep brain stimulation; DHPs, dihydropyridines; ER, endoplasmic reticulum; ETC, electron transfer chain; K-ATPs, ATP-sensitive potassium channels; LC, locus coeruleus; LTCCs, L-type calcium channels; mNOS, mitochondrial nitric oxide synthase; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; ROS, reactive oxygen species; SN, substantia nigra; TCA, tricarboxylic acid cycle; TTCCs, T-type Ca^{2+} channels; UCPs, uncoupling proteins; VTA, ventral tegmental area.

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and *in vivo* (Fig. 1), as well as specific gene expression patterns (Liss & Roeper, 2010; Roeper, 2013). With respect to their distinct projections, electrophysiological properties and gene expression profiles, at least five subpopulations of SN DA and VTA DA neurons can be defined (reviewed in (Margolis et al., 2010; Ungless and Grace, 2012; Roeper, 2013)), which are differentially affected in diseases of the DA midbrain system (Wichmann et al., 2011). So-called mesostriatal SN DA neurons, projecting to the dorsal striatum, are particularly important for voluntary movement control as well as for motor learning, habit formation, goal-directed action selection and exploration (Chase et al., 2004; Balleine and O'Doherty, 2009; Jin and Costa, 2010; Redgrave et al., 2010; Costa, 2011; Schiemann et al., 2012; Everitt and Robbins, 2013) while neighboring VTA DA neurons, with axonal projections to e.g. limbic and cortical areas, play central roles in cognition, motivation, addiction, reward and aversive behavior (Margolis et al., 2010; Stuber et al., 2010; Bourdy and Barrot, 2012; Lammel et al., 2012; Ungless and Grace, 2012; Luscher, 2013; Roeper, 2013; Lammel, 2014).

In this review, we will focus on the physiology and pathophysiology of mesostriatal SN DA neurons. We will discuss the role of ion channels for defining and modulating SN DA activity patterns and for rendering these neurons particularly vulnerable to degeneration in PD. For a general introduction into ion channels, membrane potential recordings and patch-clamp techniques, we refer to respective excellent textbooks (Hille, 2001; Sakmann & Neher, 2010; Zheng & Trudeau, 2015).

MOLECULAR PATHOLOGY OF THE DA MIDBRAIN SYSTEM IN PD

In human patients, the typical motor symptoms of PD (rigor, tremor, bradykinesia/akinesia) occur late within the neurodegenerative process, when a significant number of nigrostriatal axons (an early feature in PD) as well as SN DA neuron somata are already lost (Collier et al., 2011; Shulman et al., 2011; Burke and O'Malley, 2013; Surmeier and Schumacker, 2013). Consequently, there is still no cure or causal neuroprotective therapy available, but current established PD therapies attempt to compensate the progressive loss of striatal DA by administering its precursor L-DOPA, and/or DA D2-receptor agonists (Collier et al., 2011; Gazewood et al., 2013; Olanow and Schapira, 2013). Invasive deep brain stimulation (DBS) approaches reduce tremor and improve motor symptoms of PD and of its DA-mimetic therapy (dopaminergic therapy) (Deuschl and Agid, 2013). Understanding the molecular mechanisms of function and signaling of SN DA neurons in health and disease is the prerequisite for the development of novel, neuroprotective and/or curative PD therapies that aim to slow down or stop the progressive loss of DA neurons and their striatonigral axons.

Important in this context is that DA midbrain neurons are not equally affected by the degenerative process in PD, with SN DA neurons being particularly vulnerable to PD-trigger factors (as specified below), compared to more resistant neighboring VTA DA neurons (Bjorklund and Dunnett, 2007; Schultz, 2010b). In addition, SN DA neurons expressing the calcium-binding protein calbindin (CB_{d28k}), located mainly in the dorsal tier of the SN, are less susceptible to PD-triggers and degeneration, whereas calbindin-immunonegative ventral tier SN DA neurons are most vulnerable (Fearnley and Lees, 1991; Damier et al., 1999; Collier et al., 2013). The molecular causes for this so-called selective vulnerability of DA midbrain neurons to PD-triggers and to degeneration are still unclear (Surmeier and Schumacker, 2013). However, similar degeneration patterns are present in respective animal models of PD (Collier et al., 2013), and seem to be caused by specific intrinsic properties of highly vulnerable SN DA neurons (Surmeier et al., 2012). Consequently, a similar selective and progressive loss of SN DA neurons already occurs during normal aging – although the pattern of cell loss during aging and in PD is not identical (Fearnley and Lees, 1991; Damier et al., 1999; Collier et al., 2011). Accordingly, age is the largest risk factor for the development of PD (Jagust, 2013). In addition, a variety of other PD-trigger factors have been identified – environmental factors (e.g. mitochondrial toxins such as rotenone, which is still widely used in bulk amounts for river treatment to fight fish parasites (Finlayson et al., 2014)) as well as genetic factors (e.g. PARK-genes), as summarized in detail in excellent reviews (Hirsch and Hunot, 2009; Hardy, 2010; Alves da Costa and Checler, 2011; Collier et al., 2011; Gasser et al., 2011; Surmeier et al., 2012; Moskvina et al., 2013; Ramanan and Saykin, 2013; Singleton et al., 2013; Sulzer and Surmeier, 2013). In essence, activity-related cellular Ca^{2+} load, mitochondrial DNA deletions and mitochondrial dysfunction, as well as oxidative and metabolic stress are particularly important trigger factors for PD (Bender et al., 2006; Guzman et al., 2010; Alves da Costa and Checler, 2011; Collier et al., 2011; Shulman et al., 2011; Watfa et al., 2011; Coskun et al., 2012; Surmeier and Schumacker, 2013; Checler and Alves da Costa, 2014; Parlato and Liss, 2014; Phillipson, 2014). Furthermore, orchestrated ion channel activity tightly controls electrical activity of SN DA neurons, and is crucial for both, their age-dependent physiological functions and response to pathophysiological conditions (Liss & Roeper, 2010; Surmeier et al., 2012). In particular, voltage-gated L-type Ca^{2+} channels (LTCCs), most likely the $Ca_v1.3$ subtype, as well as metabolically gated, ATP-sensitive K^+ (K-ATP) channels in SN DA neurons, not only modulate the distinct firing patterns of these neurons, but have recently also been shown to contribute to their progressive loss and to PD pathology (Liss et al., 2005; Chan et al., 2007; Mosharov et al., 2009;

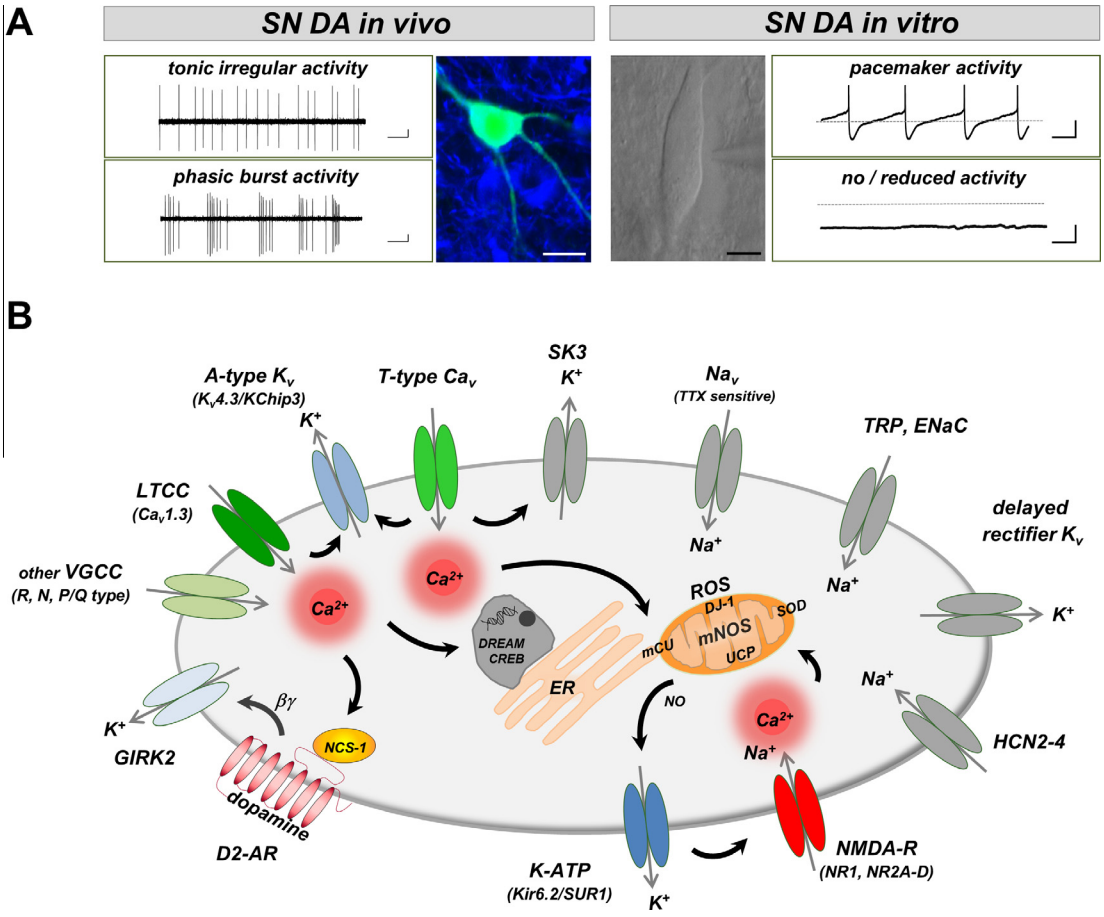

Fig. 1. Distinct activity patterns and underlying ion channel expression in substantia nigra dopamine (SN DA) neurons. (A). Typical *in vivo* and *in vitro* activity patterns of SN DA neurons from adult mice. Left: *In vivo* extracellular single-unit recordings from identified SN DA neurons recorded in anesthetized mice, displaying tonic single-spike firing (top) and phasic burst firing (bottom); scale bars = 0.5 s, 0.2 mV. Multi-fluorescence, confocal microscopy image of a neurobiotin-labeled (green), tyrosine hydroxylase (blue) immunopositive SN DA neuron after *in vivo* recording and juxtacellular labeling. Scale bar = 25 μm. Right: vital SN DA neuron in an acute coronal mouse midbrain slice, with the patch-pipette approaching the cell. Scale bar = 15 μm. Perforated-patch current-clamp recordings of an SN DA neuron *in vitro*, firing in pacemaker mode (top) and of a hyperpolarized SN DA neuron showing no spontaneous activity (bottom). Dotted lines at −40 mV; scale bars = 0.5 s, 25 mV. (B) Schematic illustration of distinct ion channels in SN DA neurons that generate or modulate their activity patterns *in vivo* and *in vitro*, and are associated with oscillating Ca^{2+} levels and elevated metabolic mitochondrial stress levels (see text for details). Note that only a selection of ion channels and mechanisms is depicted. The A-type potassium channel β-subunit KChip3, also known as transcription factor DREAM, can regulate SN DA gene expression by Ca^{2+}-dependent binding to nuclear DRE elements (similar as Ca^{2+} dependent CREB/CRE regulation of gene expression). *Abbreviations:* VGCC: voltage-gated calcium channels; LTCC (Ca_v1.3): Ca_v1.3 L-type voltage-gated calcium channel; K_v4.3/KChip3: A-type voltage-gated potassium channel; TTCC: T-type voltage-gated calcium channel; SK3: small conductance, calcium-sensitive potassium channel; Na_v: tetrodotoxin (TTX)-sensitive voltage-gated sodium channel, TRP: transient receptor potential channel; ENaC: epithelia sodium channel; HCN: hyperpolarization and cyclic nucleotide-gated cation channel; NMDA-R; N-methyl-D-aspartate glutamate receptor; K-ATP: ATP-sensitive potassium channel; Kir6.2: inwardly rectifying potassium channel; SUR1: sulfonylurea receptor; D2-AR: dopamine D2-autoreceptor; GIRK2: G-protein-coupled inwardly rectifying potassium channel; NCS-1: neuronal calcium sensor 1; DREAM: DRE antagonist modulator; CREB: cAMP response element-binding protein; ER: endoplasmic reticulum; mCU: mitochondrial calcium uniporter; ROS: reactive oxygen species; mNOS: mitochondrial nitric oxide synthase, NO: nitric oxide; UCP: uncoupling protein; DJ-1: Parkinson's disease protein 7 (PARK7); SOD: superoxide-dismutase.

Guzman et al., 2010; Liss & Roeper, 2010; Schiemann et al., 2012; Surmeier et al., 2012; Dragicevic et al., 2014). There is also emerging evidence for other ion channels, like voltage-gated T-type Ca^{2+} channels (TTCCs), particularly in the STN (Zhang et al., 2013; Yang et al., 2014), and Ca^{2+}-sensitive, voltage-gated A-type K^+ channels (Liss et al., 2001; Turner and Zamponi, 2014) that contribute – in interplay with LTCCs and K-ATP channels – to basal ganglia dysfunction, selective SN DA pathophysiology and PD, as we summarize in this review.

DISTINCT ACTIVITY PATTERNS OF SN DA NEURONS – ROLE OF ION CHANNELS

In order to fully comprehend the crucial roles of ion channels for SN DA function in health and disease, one needs to understand their fundamental role for the generation of neuronal electrical activity patterns. SN DA neurons are spontaneously active (Grace and Bunney, 1984a,b), and their tonic action potential firing is crucial for DA release from striatal axon terminals as well as from soma and dendrites of SN DA neurons (Rice et al., 2011). *In vivo*, within the intact basal ganglia

network, SN DA neurons display predominantly two types of firing patterns (Fig. 1A, left): tonic irregular single-spike activity in the frequency range of 1–10 Hz (Grace and Bunney, 1984b), or phasic burst activity at higher frequencies (~13–20 Hz in anesthetized animals, or up to 80 Hz in awake animals or humans) (Grace and Bunney, 1984a; Bayer et al., 2007; Tepper and Lee, 2007; Ishida et al., 2009; Lee & Tepper, 2009; Zaghloul et al., 2009; Drion et al., 2010; Schiemann et al., 2012). The onset of burst activity is classically defined as two consecutive spikes with an interspike interval (ISI) < 80 ms, and a burst lasts until an ISI exceeds 160 ms (80/160-ms criterion; (Grace and Bunney, 1984a)). *In vitro* (Fig. 1A, right), in synaptic isolation, SN DA neurons predominantly display an intrinsically generated, regular, so-called pacemaker activity, with relatively low frequency (~0.5–3 Hz) (Bean, 2007a; Ford and Williams, 2008; Lammel et al., 2008; Margolis et al., 2010; Drion et al., 2011; Ungless and Grace, 2012; Branch et al., 2014). Tonic irregular or pacemaker SN DA neuron firing is associated with tonic baseline DA release (Rice et al., 2011), thereby enabling basic motor activity (Surmeier and Schumacker, 2013). In contrast, burst activity of SN DA neurons causes phasic supralinearly increased DA release in response to novel, unexpected or salient events, and encodes so-called "*Go*" signals facilitating movement initiation and motor learning and reward prediction (Chase et al., 2004; Schultz, 2007; Bromberg-Martin et al., 2010; Jin and Costa, 2010; Costa, 2011; Morikawa and Paladini, 2011). Interestingly, in awake PD patients, SN DA neurons seem to display an about twofold increase in burst activity, while their mean firing frequency is not elevated (Zaghloul et al., 2009; Schiemann et al., 2012). This increase in SN DA burst activity could reflect a homeostatic compensation for the progressive loss of SN DA neurons and DA release capacity in the course of PD.

The complex and age-dependent interplay of how distinct types of ion channels and receptors shape these activity patterns of SN DA neurons is illustrated in Fig. 1B, and reviewed in detail elsewhere (Chan et al., 2007; Khaliq and Bean, 2010; Liss & Roeper, 2010; Margolis et al., 2010; Surmeier et al., 2012; Ungless and Grace, 2012; Dufour et al., 2014). Here, we focus on the roles of LTCCs and K-ATP channels in SN DA neurons for their physiological functions and involvement in PD pathology. We will offer an explanation how these two ion channels can cause and transduce PD-trigger factors, like activity-dependent and Ca^{2+}-related metabolic stress, and thus define SN DA neurons particularly vulnerable to degeneration in PD.

FUNCTIONAL ROLES OF LTCCS IN SN DA NEURONS

Role of LTCCs for SN DA pacemaker activity?

Brain LTCCs contain pore-forming $Ca_v1.2$ or $Ca_v1.3$ subunits in complex with an accessory β and α2-δ subunit (Catterall et al., 2005; Dolphin, 2006). Both isoforms are also expressed in SN DA neurons (Olson et al., 2005; Chan et al., 2007; Dragicevic et al., 2014). LTCCs are active during SN DA spike activity (Lipscombe et al., 2004), and they generate activity-associated, calcium-mediated slow oscillatory potentials, SOPs (Puopolo et al., 2007; Guzman et al., 2009; Putzier et al., 2009). However, LTCCs also substantially contribute to the oscillatory calcium influx during the interspike interval (ISI) between two action potentials (Bean, 2007a; Bean, 2007b). This is most likely due to $Ca_v1.3$ channel activity, which can activate at negative membrane potentials (Koschak et al., 2001; Putzier et al., 2009; Striessnig et al., 2014). Both LTCCs are pharmacologically blocked by dihydropyridines (DHPs, channel inhibitors that prevent calcium permeation through the channel pore (Striessnig et al., 1998), like isradipine (Snutch et al., 2001; Catterall et al., 2005; Striessnig et al., 2006; Adams and Snutch, 2007; Surmeier et al., 2010; Coca et al., 2013)). Block of LTCCs (with 5 μM isradipine or 1 μM nimodipine) in SN DA neurons can abolish the SOPs in young adult mice (PN21-32) *in vitro*, without affecting their pacemaker activity (Puopolo et al., 2007; Guzman et al., 2009). A causal contribution of LTCCs to generation or modulation of pacemaker activity in mature SN DA neurons is still controversial. More precisely, a postnatal age-dependent switch from HCN (hyperpolarization-activated cyclic nucleotide gated) cation channel-driven pacemaking in juvenile mouse SN DA neurons to $Ca_v1.3$ LTCC-driven pacemaking in adult SN DA neurons has been suggested. Due to the metabolically more challenging Ca^{2+} load, the latter pacemaker mode would render SN DA neurons more vulnerable to PD-triggers. However, this finding is highly disputed and seems to depend on used DHP concentrations and recording conditions of individual laboratories (Chan et al., 2007; Puopolo et al., 2007; Bean, 2007b; Guzman et al., 2009; Putzier et al., 2009; Liss & Roeper, 2010; Drion et al., 2011; Branch et al., 2014). Under our experimental conditions (*in vitro* brain slices of PN13 and PN90 C57BL/6 male mice; acute LTCC block by 300 nM isradipine, or chronic $Ca_v1.3$ LTCCs deficiency in $Ca_v1.3$ KO mice), LTCCs were not required for SN DA pacemaker activity – neither in juvenile nor adult mice (Dragicevic et al., 2014). However, we and others observed that LTCC activity seems to enhance the robustness of SN DA neurons to sustain spiking, e.g. in response to altered extrinsic inputs (Guzman et al., 2009). Of great pathophysiological relevance is the finding by Surmeier and colleagues that during pacemaking LTCCs participate in the generation of dendritic Ca^{2+} oscillations. The LTCC contribution to this Ca^{2+} transients increases with distance from the soma and is selective for SN DA but not VTA DA neurons of PN21–30 mice (Guzman et al., 2010; Dryanovski et al., 2013). These isradipine-sensitive (5 μM) Ca^{2+} oscillations cause a flickering of the mitochondrial membrane potential in SN DA but not VTA DA neurons, and are generating respective oscillating high levels of oxidative stress (Mosharov et al., 2009; Guzman et al., 2010; Surmeier et al., 2011). In response to this LTCC-induced oscillating oxidative stress, presumably caused by $Ca_v1.3$ channels, SN DA neurons engage defense mechanisms,

which can reduce levels of reactive oxygen species (ROS). These include intracellular endoplasmic reticulum (ER) and mitochondrial Ca^{2+} buffering, transient mild mitochondrial uncoupling (by uncoupling proteins, UCPs), and antioxidative mechanisms mediated by PARK-gene function, e.g. DJ-1 (PARK7) (Guzman et al., 2010; Sanchez-Padilla et al., 2014).

In summary, $Ca_v1.3$ and $Ca_v1.2$ LTCCs are active selectively in SN DA neurons during pacemaking, and they cause an oscillating calcium burden inducing mitochondrial stress. This renders SN DA neurons particularly vulnerable to degeneration by known PD-triggers (e.g. PARK-gene mutations, toxins). However, as LTCC function is *not* essential for SN DA pacemaker activity (but seems to contribute to its robustness) the question remains, why SN DA neurons need LTCCs in contrast to VTA DA neurons, and what could be their physiological role.

LTCCs as homeostatic gatekeepers: SN DA activity control via D2-autoreceptor modulation

Recently, we identified a novel physiological role of $Ca_v1.3$ LTCCs selectively in SN DA neurons for modulating somatodendritic D2-autoreceptor (D2-AR) function via the neuronal calcium sensor 1 (NCS-1) (Dragicevic et al., 2014). G-protein-coupled somatodendritic D2-ARs reduce activity and excitability of DA neurons, in response to local, somatodendritically released DA acting in a negative feedback (Ford et al., 2010; Ford, 2014) through activation of G-protein-coupled, inwardly rectifying potassium channels (GIRK2 = Kir3.2) (Luscher and Slesinger, 2010). Compared to VTA DA neurons, SN DA neurons from adult mice display prominent, non-desensitizing D2-AR responses (Lammel et al., 2008; Margolis et al., 2010). This response undergoes postnatal maturation: in contrast to adult SN DA neurons, D2-AR responses in PN13 SN DA neurons display pronounced desensitization (Dragicevic et al., 2014). Surprisingly, this maturation of D2-AR responses is absent in PARK7 KO (DJ-1) or PARK8 transgenic (LRRK2-R1441C) mice, where adult SN DA neurons still display juvenile-like desensitizing D2-AR responses (Goldberg et al., 2005; Tong et al., 2009; Tong and Shen, 2012). In juvenile SN DA neurons, transient high-dopamine states, induced by a single *in vivo* administration of L-DOPA or cocaine (an inhibitor of plasma membrane DA transporter (Ritz et al., 1987)), induced sensitized D2-AR responses, an effect not observed in VTA DA neurons (Dragicevic et al., 2014). These sensitized D2-AR responses were isradipine-sensitive in wildtype, as well as in $Ca_v1.2DHP^{-/-}$ mice (expressing $Ca_v1.2$ LTCCs insensitive to DHPs (Sinnegger-Brauns et al., 2004; Striessnig and Koschak, 2008)). These findings pinpoint to $Ca_v1.3$ LTCCs as crucial players for this altered inhibitory effect of DA in response to *in vivo* transient high-dopamine states. We further demonstrated that in addition to $Ca_v1.3$ LTCC function, calcium-dependent interaction of NCS-1 with D2-ARs was crucial for the sensitized, adult-like D2-AR control of SN DA activity (Dragicevic et al., 2014). NCS-1/D2-R interaction prevents D2-R desensitization by preventing G protein-coupled receptor kinase 2 (GRK2)-mediated phosphorylation of D2-R and thus β-arrestin-mediated receptor-internalization (Beaulieu and Gainetdinov, 2011; Kabbani et al., 2012). In summary, LTCCs in interplay with NCS-1 can adapt SN DA activity to extracellular DA levels via calcium-dependent modulation of D2-AR signaling (see Figs. 1 and 2; (Dragicevic et al., 2014)). In other words, $Ca_v1.3$ LTCCs can act as homeostatic gatekeepers by controlling sensitized D2-ARs responses, thus reducing SN DA activity associated DA release in response to elevated extracellular DA levels (Dragicevic et al., 2014). This may allow them to control overexcitability and to adapt motor function within the basal ganglia network. Indeed, we detected elevated mRNA levels of D2-AR, GIRK2 and NCS-1 in remaining human SN DA neurons from PD patients, compared to controls, pointing to a similar signaling network in humans that might contribute to PD pathology (Fig. 3 and (Dragicevic et al., 2014)).

Contribution of LTCCs in SN DA neurons to PD pathology

LTCC activity and related calcium signaling however comes at a high price, since it burdens SN DA neurons with an oscillatory calcium load, associated with their electrical activity (Guzman et al., 2010; Surmeier et al., 2011). In highly vulnerable SN DA neurons, this oscillatory intracellular calcium is only weakly buffered due to the absence or low levels of calcium-binding proteins, such as calbindin (CB_{d28k}) ((Hurley et al., 2013; Yamada et al., 1990; Tan et al., 2000) and compare Fig. 3). Instead, internal free calcium is taken up by the ER and mitochondria (Eisner et al., 2013; Hajnoczky et al., 2014). Mitochondrial calcium uptake is mediated by calcium transporters (in particular by the mitochondrial calcium uniporter mCU and by uncoupling proteins, UCPs (Perocchi et al., 2010; Baughman et al., 2011; De Stefani et al., 2011; Drago et al., 2011; Waldeck-Weiermair et al., 2011; Mallilankaraman et al., 2012)). Through activation of e.g. enzymes of the tricarboxylic acid cycle (TCA), calcium can increase activity of the electron transfer chain (ETC) – and thus increase generation of ROS and metabolic stress (McCormack et al., 1990; Sanchez-Padilla et al., 2014). At higher mitochondrial calcium levels, calcium also stimulates a mitochondrial nitric oxide synthase (mNOS), leading to increased nitric oxide (NO) levels, and possibly inhibition of complex IV of the ETC (cytochrome oxidase) (Traaseth et al., 2004; Murphy, 2009; Sanchez-Padilla et al., 2014). Thus, in a negative feedback-loop, higher mitochondrial calcium levels could slow down the ETC and mitochondrial calcium uptake (Sanchez-Padilla et al., 2014). However, this feedback mechanism also stimulates the production of superoxide anions, which further elevates oxidative stress levels due to calcium and LTCC function ($Ca_v1.2$ and in particular $Ca_v1.3$). This has recently been elegantly shown for locus coeruleus (LC) neurons, also displaying a high vulnerability to degeneration in PD (Sanchez-Padilla et al., 2014). It is very likely that a similar mechanism is also present in SN DA neurons, thereby contributing to compromised mitochondrial and bioenergetic function

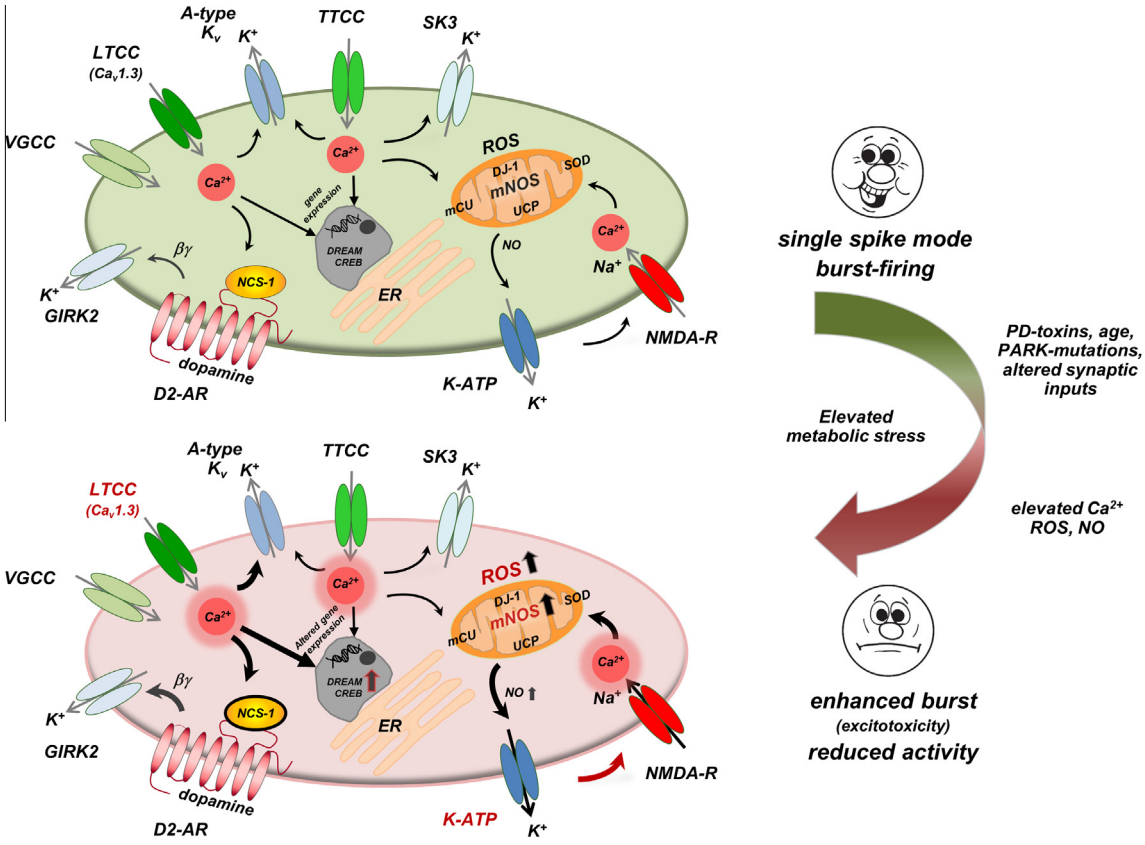

Fig. 2. Possible network of ion channel functions in SN DA neurons in health and Parkinson's disease (PD) states. Top: Activity-dependent Ca^{2+} load due to activity of LTCCs and other VGCC, in interplay with K-ATP/NMDA-R mediated burst activity, and Ca^{2+} stimulated tricarboxylic acid cycle and mNOS, creates a high metabolic burden (ROS) for SN DA neurons that is under physiological conditions controlled by several feedback mechanisms, like ER and mitochondrial Ca^{2+} buffering, mild mitochondrial membrane potential uncoupling (UCP), antioxidative enzymatic mechanisms (e.g. DJ-1, SOD function), as well as Ca^{2+} and/or metabolically controlled stimulation of ion channels that reduce SN DA electrical activity (e.g. D2-AR/NCS-1/GIRK2, K-ATP, SK3, and A-type K^+ channels) and Ca^{2+}-dependent gene-expression. Bottom: If metabolic stress levels (and related levels of Ca^{2+}, ROS and NO) are further elevated (e.g. due to PD-trigger factors, like PD-toxins, PARK-gene mutations, age-related accumulation of mitochondrial deletions/dysfunction, or altered excitatory synaptic inputs), these control mechanisms might no longer be sufficient, leading to pathophysiologically altered SN DA activity, altered gene-expression, and finally cell death (for details, see text). *Abbreviations:* same as in Fig. 1.

(Kelly, 2011; Sahin et al., 2011; Exner et al., 2012), rendering them more vulnerable to PD-trigger factors and degeneration.

Consequently, pharmacological inhibition of LTCC function in SN DA neurons might offer a novel neuroprotective strategy for PD, potentially inhibiting complex calcium-signaling and associated mitochondrial stress in SN DA neurons, and thereby reducing their high susceptibility to degeneration (Surmeier et al., 2010). LTCC blockers are already well-established drugs, and are commonly prescribed to treat hypertension in clinical practice (Epstein et al., 2007; Exner et al., 2012; Coca et al., 2013). Indeed, retrospective epidemiological studies demonstrated that systemic administration of blood–brain-barrier permissive LTCC blockers of the DHP-type (like isradipine) reduce the relative risk for developing PD of about 30 % (Becker et al., 2008; Ritz et al., 2010; Simuni et al., 2010; Marras et al., 2012; Pasternak et al., 2012; Parkinson Study, 2013). However, reliable prospective studies are still missing, and not all epidemiologic studies report PD-protective effects of LTCC blockers (Ton et al., 2007; Louis et al., 2009; Simon et al., 2010). It is noteworthy, that in all of these three studies, no stratification for exclusive DHP treatment was made, but data were pooled for both DHP and non-DHP calcium channel blockers.

In neurotoxic animal models of PD (MPTP, 6-OHDA), DHP LTCC blockers indeed seem to protect SN DA neurons from degeneration in mice (Kupsch et al., 1995; Chan et al., 2007) and non-human primates (Kupsch et al., 1996) in a dose-dependent manner (Ilijic et al., 2011), but these findings need to be confirmed in further studies. The systemic DHP-plasma levels reached in mice for SN DA protection seem to be similar to those described in humans when treated for high blood pressure (2–4 ng/ml in mice and 1–2 ng/ml in humans at 10 mg/day (Surmeier et al., 2011; Surmeier and Schumacker, 2013)). It is noteworthy that the human epidemiologic or mouse *in vivo* studies show a SN DA protective effect of systemic LTCC-blockers, but they do not demonstrate that this protective effect is a direct consequence of inhibiting SN DA LTCCs and related calcium signaling at these therapeutic plasma levels. However, work from Surmeier and colleagues provides

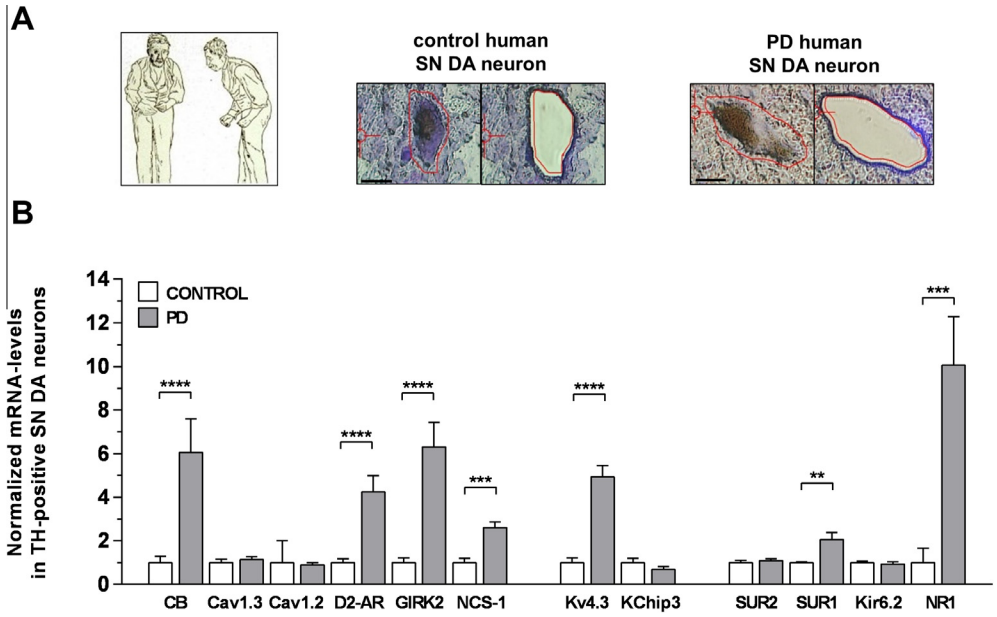

Fig. 3. Elevated mRNA-levels of distinct ion channel subunits and Ca^{2+}-binding proteins in human SN DA neurons in Parkinson's disease. (A) Individual, human neuromelanin- and tyrosine hydroxylase-positive SN DA neurons were laser-microdissected from human *post mortem* midbrain sections of control and PD brains (scale bars = 20 μm, adapted from Schiemann et al., 2012 and Dragicevic et al., 2014), and subjected to reverse transcription and quantitative PCR (RT-qPCR) analysis as described (Grundemann et al., 2011; Schlaudraff et al., 2014). (B) Cell-specific RT-qPCR analysis identified elevated mRNA-levels of the Ca^{2+}-binding proteins calbindin (CB) and NCS-1, as well as of D2-AR, GIRK2, K_v4.3, SUR1 and the NMDA-R pore forming subunit NR1 in remaining tyrosine hydroxylase (TH)-positive SN DA neurons from PD patients, compared to those of controls (Schlaudraff, 2010; Schiemann et al., 2012; Dragicevic et al., 2014). Thus, SN DA-specific ion channel functions identified in mice might also be present in human SN DA neurons and contribute to PD-pathology. For details, see text. *Abbreviations:* same as in Fig. 1.

evidence that this might indeed be the underlying protective mechanism. They have shown that isradipine (200 nM) reduces oxidative stress levels and mitochondrial membrane potential flickering, associated with LTCC activity in SN DA neurons that is elevated in PARK7 (DJ-1) KO mice (Guzman et al., 2010; Surmeier et al., 2011). Also, isradipine (1 μM) inhibited calcium-related oxidative stress levels due to mNOS activity in LC neurons (Sanchez-Padilla et al., 2014).

Based on these findings, blood–brain-barrier permeable LTCC blockers (ideally administered very early or before PD-symptoms manifest, and most SN DA neurons are lost) are already in clinical trials as a novel neuroprotective therapeutic strategy in PD (ClinicalTrials.gov Identifier: NCT00909545, (Simuni et al., 2010; Parkinson Study, 2013)). Given the described complex beneficial, as well as detrimental effects of LTCCs on calcium signaling pathways in SN DA and other neurons, unpredictable side effects of chronic pharmacological LTCC block might occur, however DHPs are already prescribed long term to many patients to treat hypertension without significant problems. Nevertheless, neuron-type-, LTCC-isoform- and splice-variant-specific (Koschak, 2010; Bock et al., 2011; Hofmann et al., 2014; Lieb et al., 2014), blood–brain–barrier permeable blockers, or selective blockers of detrimental calcium signaling downstream of LTCCs would be required for tailored PD-preventive therapy. Indeed, novel identified Ca_v1.3 selective LTCC antagonists, pyrimidinetriones (PYTs), have recently been reported as potential new therapeutics for PD (Kang et al., 2012; Kang et al., 2013). But it is currently unclear under which conditions they act as Ca_v1.3-selective inhibitors or possibly even activators (Huang et al., 2014; Ortner et al., 2014), and their PD-protective effect has not yet been demonstrated in clinical studies.

FUNCTIONAL ROLES OF K-ATP CHANNELS IN SN DA NEURONS

Role of SN DA K-ATP channels for burst activity and novelty-related behavior

K-ATP channels in SN DA (and VTA DA) neurons in adult mice and in humans are formed by four pore-forming, inwardly rectifying Kir6.2 subunits and four regulatory SUR1 subunits (sulfonylurea receptor, ABC-transporter superfamily) (Nichols, 2006; Liss & Roeper, 2010). K-ATP channels have first been described in pancreatic ß-cells, where their closure in response to rising blood glucose levels – and concomitantly increased intracellular ATP levels – is triggering insulin secretion (Ashcroft et al., 1984; Nichols, 2006; Clark and Proks, 2010; Seino, 2012). Moreover, K-ATP channels are active in a variety of different cell types and are ubiquitously expressed throughout the brain and other tissues (Liss et al., 2005; Nichols, 2006; Ashcroft, 2007). K-ATP channels are pharmacologically blocked by sulfonylureas such as glibenclamide or tolbutamide (Amoroso et al., 1990; Gomis and Valdeolmillos, 1998; Kanno et al., 2002; Bryan et al., 2005; Ashcroft, 2007), and their activity is physiologically regulated by a variety of metabolic signals, such as

insulin, leptin, ghrelin, long-chain fatty-acids (acyl-CoA), PIP_2, pH, hydrogen peroxide and NO (Spanswick et al., 2000; Levin et al., 2004; Lin et al., 2004; Avshalumov et al., 2007; Haider et al., 2007; Andrews et al., 2009; Leinninger et al., 2009; Opland et al., 2010; Fioramonti et al., 2011; Levin et al., 2011; Rice, 2011). In essence, the open probability of K-ATP channels generally increases in metabolic demand situations, and this leads to hyperpolarized membrane potentials and reduced electrical activity (Nichols, 2006; Ashcroft and Rorsman, 2013). By this mechanism, K-ATP channels adapt energy-demanding electrical activity of excitable cells to their metabolic states, and can protect neurons from overexcitability and excitotoxicity, e.g. in ischemic preconditioning (Liss and Roeper, 2001; Yamada and Inagaki, 2005; Soundarapandian et al., 2007).

For SN DA neurons, we have recently identified a novel specific physiological role of K-ATP channels. In a subpopulation of medial SN DA neurons, projecting to the dorsomedial striatum, K-ATP channel activity facilitates the switch from tonic firing to NMDA glutamate receptor (NMDA-R)-mediated burst activity *in vivo* (Johnson et al., 1992; Johnson and Wu, 2004; Deister et al., 2009; Zweifel et al., 2009; Schiemann et al., 2012). More precisely, in adult global Kir6.2 knock-out (KO) mice (Minami et al., 2004), or in adult WT mice after cell-selective, virus-mediated silencing of K-ATP channel function, phasic burst firing of medial SN DA neurons *in vivo* was decreased about two-fold, without changes in tonic firing rates (Schiemann et al., 2012). In the same study, we demonstrated that pharmacological co-activation of K-ATP channels and NMDA receptors was sufficient to induce burst firing *in vitro* in medial SN DA neurons. K-ATP channels could gate NMDA-R-mediated bursting in SN DA neurons by providing a hyperpolarizing component as described (Gomis and Valdeolmillos, 1998; Kanno et al., 2002; Shen and Johnson, 2010; Schiemann et al., 2012), necessary for *in vitro* SN DA burst activation by NMDA (Johnson et al., 1992; Johnson and Wu, 2004). However, future studies are required to reveal the detailed mechanisms underlying K-ATP channel-gated bursting.

Beyond that, we could show that K-ATP channel-gated burst firing in medial SN DA neurons was necessary for novelty-induced exploration *in vivo.* Kir6.2 KO mice, or WT mice after cell-selective silencing of medial SN DA K-ATP channels, displayed significantly reduced novelty-induced exploratory behavior (da Silva and Costa, 2012; Schiemann et al., 2012). Consequently, K-ATP channels in these neurons could integrate multiple metabolic signals and transduce them into their open-probability, and thereby tune and adapt *in vivo* burst activity and related behavior to distinct metabolic demands.

In summary, K-ATP channels trigger burst firing in a subpopulation of medial SN DA neurons, leading to phasic DA release, and to associated (dopamine D1 receptor-dependent) exploration and goal-directed behavior in response to novel situations and contextual changes (Frank et al., 2004; Rutledge et al., 2009; Schiemann et al., 2012). Consistent with these findings in rodents, recent human functional brain imaging data revealed that a corresponding rostromedial part of the medial SN/VTA midbrain complex in humans is indeed strongly and selectively activated by novel, but non-rewarding stimuli (Krebs et al., 2011). These findings indicate that K-ATP channels in human SN DA neurons may have a similar role for promoting burst activity and novelty-related behavior.

K-ATP channels as metabolic gatekeepers: SN DA activity control in response to metabolic stress

As described, K-ATP channels integrate and transduce a variety of metabolic signals into their specific open probability. Thus, these channels act as metabolic gatekeepers, adapting SN DA activity to the metabolic state of these cells (or the organism) based on two different strategies: I) in context of the above described K-ATP channel-mediated burst facilitation in SN DA neurons, metabolic demand situations would increase the open probability of K-ATP channels and thus enhance burst activity of SN DA neurons as well as exploratory behavior (e.g. to find novel food sources). II) if K-ATP channel activity is further increased in SN DA neurons, e.g. due to enhanced oxidative mitochondrial stress, mitochondrial dysfunction, elevated calcium levels or PD-toxins (like MPTP or rotenone), the resulting membrane potential hyperpolarization will at some point inevitably lead to reduced activity, or even silencing of the cell, as we demonstrated *in vitro* in adult mice (Liss et al., 2005). Reduced SN DA activity would be beneficial in metabolic stress situation in the short run, as it reduces metabolically demanding burst firing, as well as the activity of the highly ATP consuming N^+/K^+ ATPase, which is stimulated by electrical activity (Johnson et al., 1992). However in the long run, reduced electrical activity could be detrimental for SN DA neurons, as detailed below. In this context, it is important to note that even though both, SN DA as well as VTA DA neurons express functional K-ATP channels of the same molecular make-up (Kir6.2/SUR1), their metabolic sensitivity and thus open probability is intrinsically higher in vulnerable SN DA neurons due to a lower degree of physiological mitochondrial uncoupling (lower expression of the uncoupling protein UCP2) (Liss et al., 2005). Indeed, mild pharmacological mitochondrial uncoupling or superoxide-dismutase mimetics can reduce generation of ROS and reduce K-ATP channel open probability, without compromising ATP production in SN DA neurons (Liss et al., 2005).

Contribution of K-ATP channels in SN DA neurons to PD pathology

K-ATP channels in highly vulnerable SN DA neurons are particularly sensitive to metabolic stress, caused in animal models e.g. by PD-trigger factors such as the mitochondrial complex I blockers MPTP or rotenone (Liss et al., 2005). The resulting increased activity of K-ATP channels due to pathophysiological metabolic stress

leads to membrane potential hyperpolarization and reduced SN DA activity (Liss et al., 2005). This adaptive response might be beneficial in acute scenarios as described. However, chronic pathophysiological activation of K-ATP channels in SN DA neurons in response to chronic *in vivo* PD-toxins has been shown not to be beneficial but to trigger their selective degeneration (Liss et al., 2005). More precisely, genetic inactivation of K-ATP channels in global Kir6.2 KO mice resulted in a selective and complete rescue of adult SN DA neurons in a chronic low-dose *in vivo* MPTP PD-model (Liss et al., 2005; Meredith and Rademacher, 2011). Moreover, loss of K-ATP channels induced a similar selective rescue of highly vulnerable SN DA (but not VTA DA) neurons in a mechanistically different, genetic model of selective SN DA degeneration, the *weaver* mouse (*Girk2wv/wv*) (Liss et al., 2005). In cell culture, the K-ATP channel blocker glibenclamide (30–100 μM) protected DA neurons in juvenile rats (PN15) from PD-triggers and degeneration – presumably via disrupting their mitochondrial calcium homeostasis (Toulorge et al., 2010).

In addition, our data for human SN DA neurons further point to a role of K-ATP channels for PD pathology: we found that remaining SN DA neurons from PD patients compared to those of controls express about twofold higher levels of the K-ATP channel subunit SUR1, responsible for channel trafficking to the plasma membrane (Tucker et al., 1997; Sharma et al., 1999), as well as about 10-fold higher levels of the NMDA-R pore forming subunit NR1 (compare Fig. 3 and (Schiemann et al., 2012)). In accordance with the described K-ATP NMDA-R interplay for triggering burst firing in mouse SN DA neurons, human SN DA neurons of PD patients seem to display high levels of bursting, as recorded in awake patients during DBS (Zaghloul et al., 2009; Schiemann et al., 2012) – possibly as a compensatory response to the progressive loss of SN DA neurons. Moreover, reduced novelty seeking, as well as reduced exploratory excitability have been documented for PD patients (Bodi et al., 2009; Rutledge et al., 2009). However, high levels of metabolically demanding (compensatory) burst activity will also further increase metabolic stress in these neurons, as described.

Taken together, these rodent and human data suggest that pharmacological blockade of K-ATP channels in SN DA neurons might provide another novel neuroprotective strategy for PD. Pharmacological K-ATP channel blockers (like glibenclamide) are – similar to LTCC blockers – already well-established and widely used drugs to treat type 2 diabetes (T2D) (Ashcroft, 2007; Ashcroft and Rorsman, 2013). And there is evidence for a certain blood–brain barrier penetrance of these drugs (Ashcroft, 2010). Indeed, retrospective meta-analyses revealed epidemiological evidence of a reduced risk for PD in T2D patients treated with K-ATP channel blockers (Powers et al., 2006; Scigliano et al., 2006; Schernhammer et al., 2011; Wahlqvist et al., 2012; Cereda et al., 2013; Lu et al., 2014). However, statistical analysis is complicated by the fact that T2D per se seems to increase the risk for PD (Hu et al., 2007; Lima et al., 2014; Zhang and Tian, 2014), and there is evidence that T2D and PD might share similar disease pathways (Santiago and Potashkin, 2013). To our knowledge, K-ATP channel blockers are currently not systematically tested as a novel neuroprotective strategy in PD. And similarly as for LTCCs blockers, given the widespread functional expression of K-ATP channels, SN DA and K-ATP subtype-specific drugs would be desired. However, the NMDA-R antagonist memantine is in trial for PD therapy and seems to be beneficial (Emre et al., 2010). Interestingly, memantine also acts as a K-ATP channel blocker, and affect SN DA burst firing, independently of NMDA-R function (Giustizieri et al., 2007).

COMPLEX ION CHANNEL INTERPLAY IN SN DA NEURONS IN HEALTH AND PD: POSSIBLE MECHANISMS AND THERAPEUTICAL IMPLICATIONS

In essence, $Ca_v1.3$ LTCCs with low voltage-activation as well as K-ATP channels with high metabolic sensitivity render SN DA neurons particularly vulnerable to PD-triggers and degeneration, as described. However, the question remains, why do SN DA neurons need these two channels that generate a high metabolic burden, while VTA DA neurons function well without depending on them? The answer is still not clear. However, here we summarize findings and offer our views and hypotheses (Fig. 2, Fig. 3) for the specific physiological roles of LTCC and K-ATP channels in SN DA neurons, as well as for the possible pathophysiological consequences of their related activity in response to PD-trigger factors.

We showed that K-ATP channel function (in interplay with NMDA-R), is crucial for triggering phasic burst activity in SN DA neurons as well as novelty-related explorative behavior of mice (Schiemann et al., 2012). This mechanism will likely, in metabolic demand situations (e.g. low blood glucose levels, hunger, or food deprivation), stimulate motor activity and exploration, increasing the chance to locate novel food sources. As a consequence, enhanced stressful burst firing and related NMDA-R activity will however further increase calcium load, related mitochondrial stress, and ROS, as well as activity-related metabolic stress as previously described (e.g. due to augmented N^+/K^+ ATPase activity in SN DA neurons). On the other hand, increased metabolic stress will further activate K-ATP channels in SN DA neurons, and thus hyperpolarize the cell, thereby providing an intrinsic control mechanism, which could prevent overexcitability and related excitotoxicity.

We propose a similar complex functional role of $Ca_v1.3$ LTCCs in SN DA neurons, as these channels are *not* crucial for generating spontaneous activity of these neurons. We hypothesize that the pulsatile calcium signals, caused by $Ca_v1.3$ channels during spontaneous activity, are essential for other physiological functions specifically of SN DA neurons (Mosharov et al., 2009). On one hand, LTCC-mediated calcium influx will directly activate calcium dependent enzymes, like e.g. those of the TCA (Plaitakis and Shashidharan, 2000; Carafoli, 2010) and mNOS

(Sanchez-Padilla et al., 2014). On the other hand, LTCC-mediated calcium influx will stimulate or repress gene expression, selectively in SN DA neurons, via direct or indirect calcium-dependent modulation of gene transcription (West et al., 2001), e.g. via CREB (cAMP response element-binding protein) and DREAM (DRE antagonist modulator) pathways (Mandel and Goodman, 1999; Osawa et al., 2001; Screaton et al., 2004; Rivas et al., 2011; Zhang et al., 2011; Selvakumar et al., 2014). Similar as K-ATP-mediated burst activity, this physiological LTCC-function creates however, a high metabolic burden for SN DA neurons. Consequently, intrinsic negative feedback control mechanisms are again present to prevent LTCC-mediated overexcitability and excitotoxicity: elevated internal calcium levels lead to enhanced NCS-1-mediated sensitization of D2-AR function in SN DA neurons, and thus increased GIRK2 K^+ channel-mediated hyperpolarization and DA autoinhibition of electrical activity (Dragicevic et al., 2014).

An additional calcium-sensitive feedback mechanism could be provided by calcium and voltage-sensitive A-type K^+ channels (Jerng and Pfaffinger, 2014). In SN DA neurons, these channels are built by $K_v4.3$ pore-forming subunits and regulatory calcium-sensing KChip3 subunits (Liss et al., 2001), also members of the NCS-1 family (Figs. 1–3; (An et al., 2000; Jerng and Pfaffinger, 2014; Turner and Zamponi, 2014)). A-type K^+ channels inhibit pacemaker activity of SN DA but not of VTA DA neurons by prolonging the interspike interval (Liss et al., 2001; Liss and Roeper, 2002; Lammel, 2004) with increased inhibitory effects with elevated levels of free intracellular calcium (Jerng and Pfaffinger, 2014). KChip3, also known as the calcium-dependent transcriptional repressor DREAM (Jo et al., 2001; Buxbaum, 2004), surprisingly does not only act as a calcium-sensing regulatory subunit of A-type K^+ channels, but e.g. can also – dependent on free intracellular calcium levels – shuttle to the nucleus and regulate gene expression (Li and Adelman, 2000; Sours-Brothers et al., 2009; Mellstrom et al., 2014). These multiple functions of KChip3 allow complex short-term and long-term adaptions of electrical activity of SN DA neurons to distinct calcium levels and homeostatic needs. Thus, calcium dependent A-type K^+ channel activity could also counteract LTCC as well as K-ATP/NMDA-R-mediated overexcitability and excitotoxicity. As a further control mechanism, KChip3/DREAM could reduce K-ATP/NMDA-R-mediated burst activity by negatively modulating NMDA-R activity (Wang and Wang, 2012). Activation of DREAM also reduces L-DOPA-induced dyskinesias in mice (Ruiz-DeDiego et al., 2014). Consequently, pharmacological modulation of A-type K^+ channels in SN DA neurons might provide another neuroprotective strategy for PD. Indeed, cell-specific data from our group show a dramatic increase of A-type K^+ channel pore-forming $K_v4.3$ mRNA in surviving human SN DA neurons from end stage PD patients, compared to controls (see Fig. 3), supporting this view of a protective A-type channel function in vulnerable SN DA neurons.

In summary, LTCC and K-ATP channel function in SN DA neurons are crucial for their specific physiological function, but they generate an activity-related metabolic burden for those neurons (Ca^{2+}, ROS and NO levels) that renders them particularly vulnerable to PD-triggers and degeneration. Consequently, as summarized in Fig. 2A, a variety of backup mechanisms are present in SN DA neurons to control and counteract LTCC and K-ATP channel-triggered overexcitability and excitotoxicity (D2-AR/GIRK2, SK3, A-type K^+ channels, K-ATP channels), or to counteract Ca^{2+}, metabolic stress and ROS (e.g. SOD, UCPs, DJ-1/PARK7, (Guzman et al., 2010; Surmeier et al., 2012)). Under physiological conditions, this complex network of activity-controlling ion channels and metabolic protection pathways, in interplay with ER and mitochondrial Ca^{2+} buffering, allows LTCC and K-ATP channel function in SN DA neurons without triggering degenerative pathways (Fig. 2A).

However, what happens if PD-triggers further contribute to this intrinsic metabolic stress of SN DA neurons? These triggers could be intrinsic PARK-gene mutations (such as DJ-1), or increased age and age-related mitochondrial dysfunction, or extrinsic factors, such as environmental toxins (e.g. rotenone MPTP), or PD-related alterations in glutamatergic synaptic input (Rodriguez et al., 1998; Hardy, 2010; Meredith and Rademacher, 2011).

As illustrated in Fig. 2B, all these PD-triggers can synergistically increase mitochondrial dysfunction, general metabolic stress and intracellular free calcium load, ROS and NO levels. At this point, a vicious circle could take its course, by further stimulating mNOS/NO-levels, and thus not only possibly reduce ETC activity (Sanchez-Padilla et al., 2014), but also elevate superoxide levels, further increasing mitochondrial stress, as described above (Surmeier et al., 2010; Sanchez-Padilla et al., 2014). NO itself as well as ROS / mitochondrial dysfunction will further increase the open probability of K-ATP channels (Zhang et al., 2001; Lin et al., 2004), which – until a certain point – will stimulate stressful bursting of SN DA neurons, and thus further drive the vicious cycle of Ca^{2+} load, metabolic stress and excitotoxicity that can no longer be properly controlled by the described inhibitory feedback mechanisms. On the other hand, in a chronic interplay of increased Ca^{2+}-dependent D2/GIRK2 and A-type K^+ channel activity, further K-ATP channel activation would rather lead to a chronic reduction of SN DA activity, as described above, and thus likely lead to a reduction of activity-dependent vital factors, like brain-derived neurotrophic factor (BDNF) (Hyman et al., 1991; Kurauchi et al., 2011; Peng et al., 2011). In either scenario, the inhibitory feedback systems in SN DA neurons, likely serving to protect from metabolically precarious physiological LTCC and K-ATP activity and related pathophysiological overexcitability, would eventually fail in the chronic presence of too high levels of metabolic stressors in PD, ultimately leading to the selective death of SN DA neurons.

CONCLUSIONS

The pathological hallmark of PD, which causes the major motor-related symptoms of the disease, is the selective

loss of mesostriatal SN DA neurons. There is clear evidence that physiological LTCC (in particular of the $Ca_v1.3$ type) as well as K-ATP channel (made up by Kir6.2/SUR1 subunits) function contribute to metabolic stress and the selective high vulnerability of SN DA neurons to degeneration in PD and its animal models. Nevertheless, these channels in SN DA (but not in VTA DA) neurons seem to be crucial for their distinct electrical activity patterns, their physiological signaling (e.g. calcium-dependent enzyme activation and regulation of gene expression), and their related complex functions within the basal ganglia network (e.g. novelty-related behavior). However, physiological K-ATP and LTCC activity generates an intrinsic high metabolic burden for SN DA neurons, due to associated burst activity and activity-dependent elevated intracellular Ca^{2+} levels. We hypothesize that consequently, a complex network of inhibitory feedback mechanisms is present in SN DA neurons to control physiological LTCC and K-ATP channel function and to homeostatically tune SN DA activity pattern to the metabolic states of these neurons, to thus circumvent overexcitability and excitotoxicity. Ca^{2+}-dependent sensitization of inhibitory D2-AR/GIRK2 signaling as well as Ca^{2+}-dependent A-type K^+ channel signaling in SN DA neurons provide just two distinct potential feedback mechanisms.

However, activity patterns of SN DA neurons are controlled by a variety of additional ion channels and receptors (compare Fig. 1), and thus this network is even more complex than described here. To further illustrate the complexity, recent evidence shows functional coupling of voltage-gated T-type Ca^{2+} channels with A-type K^+ channels ($K_v4.3$) via Ca^{2+} levels and KChip3 (Anderson et al., 2010; Turner and Zamponi, 2014), and we gained evidence for an interplay of TTCCs with LTCCs and K-ATPs. Not only in this context, it is very important to systematically study the cell-specific contributions of other voltage-gated calcium channels (like P-, N-, Q-, R-, and T-type channels (Catterall et al., 2005)) to SN DA function in health and PD. In view of desired novel neuroprotective PD-therapies, these ion channels provide promising potential targets, in addition to LTCC-blockers, which are already in clinical trials (Parkinson Study, 2013). However, as all these channels are not only expressed in SN DA neurons, but in a variety of other neuronal and non-neuronal cells, the development of channel subtype-specific blockers that ideally selectively target SN DA neurons, is desired. Future research is needed to develop those blockers, and to address acute and chronic pathophysiological consequences, as well as side effects of pharmacological modulation of the emerging complex network of ion channel functions in SN DA neurons, as potential novel therapeutic strategies in PD.

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